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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/996,484
Filing Date: November 28, 2001
Appellant(s): CHOO ET AL.

Dahna S. Pasternak
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 23 April 2007 appealing from the Office action mailed 30 October 2006.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

McEwan et al. "Mechanism of gene expression by the glucocorticoid receptor: role of protein-protein interactions." Bioessays, Vol. 19, No. 2 (Feb. 1997), pp. 153-160.

Bledsoe et al. "Crystal structure of the glucocorticoid receptor ligand binding domain reveals a novel mode of receptor dimerization and coactivator recognition." Cell, Vol. 110, No. 1 (Jul 12, 2002), pp. 93-105.

Barbas et al. "Zinc finger protein derivatives and methods therefore." (Jul. 20, 1995) WO 95/19431.

Vegeto et al. "Mutated steroid hormone receptors, methods for their use and molecular switch for gene therapy." (Nov. 25, 1993) WO 93/23431

Liu et al. "Design of polydactyl zinc-finger proteins for unique addressing within complex genomes." Proc. Natl. Acad. Sci. USA, Vol. 94, No. 11, pp. 5525-5530.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 34 is rejected under 35 U.S.C. 102(b) as being anticipated by Barbas et al. (1995) WO 95/19431[1].

Claim 34, as amended, is directed to a complex comprising: (a) a heterodimer comprising (i) a first polypeptide, and (ii) a second polypeptide; and (b) a ligand, wherein the first and second polypeptides bind to DNA, and further wherein the first or second polypeptide comprises an engineered Cys2-His2 zinc finger binding domain.

It is particularly noted that the amended claim no longer requires that the first polypeptide bind to the second polypeptide in a manner modulatable by a ligand as recited in the previously examined claims. Furthermore, the specification states at p. 49, ll. 1-2, "A ligand according to the invention is typically any molecule capable of binding to any of the other components of a switching system." Thus, the amended claim now embraces any complex comprising a heterodimer comprising a first and second DNA-binding polypeptide and anything that binds to either one of the first and second polypeptide (irrespective of whether binding of the first and second polypeptide is modulatable by the ligand), wherein either the first or second DNA-binding polypeptide comprises an engineered Cys2-His2 zinc finger binding domain.

In Example 12 (beginning at page 85), Barbas et al. teaches construction of a Zif$(C7)_6$-Jun/Zif-268-Fos heterodimer, which comprises a C7-type zinc finger linked to a Jun leucine zipper protein interaction domain and a Zif268 zinc finger linked to a Fos leucine zipper protein

[1] This rejection was originally set forth in the Final Office Action mailed 30 October 2006 and is reiterated herein.

interaction domain. As described in Example 10, the C7 zinc finger is an engineered zinc finger DNA binding domain derived from the Zif268 Cys2-His2 zinc finger. (See also Figure 8A and the caption thereto (showing the Cys2-His2 structure of Zif268 finger 1) and Figure 9 and the caption thereto (showing the modification comprised by the C7 zinc finger (leftmost column)). Thus, Barbas et al. teaches a complex comprising a heterodimer comprising first and second DNA-binding polypeptides, wherein at least one of the polypeptides comprises and engineered Cys2-His2 zinc finger DNA binding domain. On page 1, ¶4, Barbas et al. teaches that zinc finger domains are folded around a zinc ion. As the zinc ion is bound to the first and second protein moieties, zinc is a ligand according to the broadest reasonable interpretation of the claim limitation. Thus, the heterodimer of Barbas et al. comprises all of the elements of the complex claimed in the instant application. Therefore, the claimed invention is anticipated by Barbas et al.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Vegeto *et al.* WO 93/23431 as evidenced by McEwan *et al.* (1997) *Bioessays* 19:153-160 and Bledsoe *et al.* (2002) *Cell* 110:93-105 in view of Liu *et al.* (1997) *Proc. Natl. Acad. Sci. USA* 94:5525-5530[2].

Claim 48 is directed to a switching system comprising a protein switch comprising: (i) a first component comprising a first polypeptide and (ii) a second component comprising a second polypeptide, in which the first polypeptide binds to the second polypeptide in a manner modulatable by a ligand, and (iii) a third component comprising the ligand, wherein the first and second polypeptides bind to DNA, and further wherein the first or second polypeptide comprises an engineered Cys2-His2 zinc finger binding domain.

Vegeto *et al.* teaches mutated steroid hormone receptors and their use as a molecular switch for regulating expression of a nucleic acid in mammals (see especially the Abstract and the discussion commencing p. 6, ¶4 and continued through p. 7, ¶4). Vegeto *et al.* further contemplates steroid hormone receptors such as glucocorticoid receptors as among those to be used as the starting material for constructing the molecular switch (see especially p. 8, ll. 25-28). Thus, Vegeto *et al.* teaches a switching system comprising a first and second polypeptide and a ligand, wherein the first and second polypeptides bind to each other in a manner modulatable by

[2] This rejection was originally set forth in the Non-Final Office Action mailed 30 October 2006 and is substantially reiterated herein except for changes made to account for the removal of claims 34 and 49 from the rejection in subsequent actions.

the ligand (as evidenced by the teachings of McEwan *et al.* and Bledsoe *et al.*)[3]. Furthermore, Vegeto *et al.* teaches that ligand activated dimerization is a general property of steroid hormone receptors (see especially the paragraph bridging pages 1-2).

Vegeto *et al.* does not teach that a protein should comprise an engineered Cys2-His2 zinc finger binding domain. However, Vegeto *et al.* does teach, "In preferred embodiments of the molecular switch, the modified steroid receptor has both the ligand binding domain and DNA binding domain replaced" (p. 7, ll. 7-9; emphasis added) and suggests certain non-mammalian DNA binding domains.

Liu *et al.* teaches the design and construction of highly selective six finger DNA binding proteins by modification of the Cys2-His2 zinc finger domains of Zif268 and Sp1 proteins (see especially p. 5528, ¶1) and demonstrates that the polydactyl protein can bind to a contiguous 18-bp DNA sequence with high affinity and specificity (see especially Figure 2 and the caption thereto and the section entitled "Characterization of Affinity and Specificity of Two Six-Finger Proteins" commencing on page 5528). The polydactyl zinc finger proteins are also demonstrated to function in human cells to activate or repress transcription (see especially Figure 4 and the caption thereto and the section entitled "Transcriptional Activation and Repression" commencing on page 5528). Liu *et al.* further teaches that such polydactyl zinc-finger proteins should be

[3] Page 10 of the 18 April 2006 Office Action describes the teachings of McEwan et al. and Bledsoe et al. regarding glucocorticoid receptors in detail stating, "As discussed in previous Office Actions, McEwan *et al.* describes in detail the DNA binding domain comprised within the glucocorticoid receptor protein (see especially p. 3, Figure 4 and the caption thereto). Also illustrated in Figure 4 of McEwan *et al.* is the binding of the glucocorticoid receptor to DNA as a homodimer. Bledsoe *et al.* teaches, "[h]ormone binding initiates the release of chaperone proteins from the GR, allowing dimerization and translocation of the receptor into the nucleus" (second full paragraph in the right column on page 93)."

broadly applicable as genome-specific transcriptional switches in gene therapy strategies and the development of novel transgenic animals (see, e.g., the Abstract), which uses are the same as the uses contemplated by Vegeto *et al.* for the molecular switch described therein.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the molecular switch of Vegeto *et al.* to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu *et al.* Motivation to combine these teachings comes from the nature of the problem to be solved by the molecular switch of Vegeto *et al.*, which is to regulate expression of a nucleic acid in mammals (*Id.*) and from the teachings of Liu *et al.* that: a) specific delivery of a DNA-binding protein to a single site within a genome as complex as that found in humans, 3.5 billion bp, requires an address of at least 16 bp (p. 5525, bridging col. 1-2); b) although natural proteins containing long polydactyl arrays of zinc-finger domains have been inferred from sequence, no zinc-finger proteins have been demonstrated to bind such a long contiguous DNA sequence (p. 5525, bridging col. 1-2); and c) the polydactyl proteins described therein can bind to a contiguous 18-bp DNA sequence with high affinity and specificity and function in human cells to activate or repress transcription. Viewed as a whole, the skilled artisan would clearly be motivated to substitute the polydactyl DNA binding domain of Liu *et al.* for the DNA binding domains contemplated by Vegeto *et al.* for construction of a molecular switch operative in mammalian cells to obtain the expected benefit of highly specific delivery of the switch in the complex mammalian genome.

Absent evidence to the contrary, one would have a reasonable expectation of success in combining these teachings in view of the modular nature of steroid hormone receptor proteins (see especially Vegeto *et al.*, p. 2, ¶1) and the demonstration by Liu *et al.* that the DNA binding

domains disclosed therein can be fused to heterologous polypeptides and are active in mammalian cells (see especially Figure 1 and the caption thereto).

In view of these considerations, the invention of claim 48, as a whole, would have been obvious to one of ordinary skill in the art at the time the invention was made. Therefore, the claims are properly rejected under 35 USC §103(a) as obvious over the art.

(10) Response to Argument

"A. Claim 34 is not anticipated by the cited reference"

Appellants contend that claim 34 is not anticipated by Barbas because Barbas' Zif(C7)6-JunlZif-268-Fos complex is not a complex including a heterodimer component and a ligand component, as set forth in claim 34.

"1. Claim construction: 'ligand'"

Appellant contends that in construing claim 34, it must be kept in mind that "as an initial matter, the PTO applies to the verbiage of the proposed claims the broadest reasonable meaning of the words in their ordinary usage as they would be understood by one of ordinary skill in the art, taking into account whatever enlightenment by way of definitions or otherwise that may be afforded by the written description contained in the applicant's specification." *In re Morris*, 127 F.3d 1048, 1054,44 USPQ2d 1023, 1027 (Fed. Cir. 1997). Appellant urges that the teachings of the specification as a whole must be taken into account, particularly what is taught about the claim terms in the particularly claimed.

In particular, Appellant urges that the specification makes clear, with reference to

various scientific papers, that, in the claimed protein switches, protein-binding ligands are molecules made up of two or more atoms. (Citing page 49, lines 16-28 of the specification, which is quoted in full on page 5 of Appellant's brief.)

Appellant further contends, "[T]he specification also makes clear that, in the context of a complex comprising a heterodimer and a ligand (i.e., a protein switch), the ligand component of the complex is separate from the polypeptides and this separate ligand component modulates binding of the two proteins..." (Brief, page 5; citing page 10, lines 16- 19 and lines 30-33 of the specification which are quoted in full on pages 5-6 of Appellant's brief.)

Appellant concludes that the ligand component of a complex comprising a heterodimer (two polypeptides) and a ligand, as described in the specification, cannot reasonably be interpreted to be a single zinc ion and that a person of skill in the art would have understood that the ligand component of the complex of claim 34 is not a zinc ion coordinated by a zinc finger, but, rather, a molecule that is distinct from the DNA binding polypeptides and that mediates the binding of the two polypeptide molecules to each other.

Appellant's arguments have been fully considered but are not deemed persuasive. Under the heading, "THE WORDS OF A CLAIM MUST BE GIVEN THEIR 'PLAIN MEANING' UNLESS SUCH MEANING IS INCONSISTENT WITH THE SPECIFICATION" MPEP 2111.01 I. states, "Although claims of issued patents are interpreted in light of the specification, prosecution history, prior art and other claims, this is not the mode of claim interpretation to be applied during examination. During examination, the claims must be interpreted as broadly as their terms reasonably allow." (Citing *In re American Academy of Science Tech Center*, 367 F.3d

1359, 1369, 70 USPQ2d 1827, 1834 (Fed. Cir. 2004). It is further noted that the specification states, "Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art (e.g.. in cell culture, molecular genetics, nucleic acid chemistry, hybridisation techniques and biochemistry)." (Page 9, lines 26-29.)

The term "ligand" as it would be commonly understood by one of skill in the art is simply anything capable of specifically binding to the polypeptide components of the complex. Nothing in the supporting disclosure would lead one of skill in the art to the conclusion that the plain meaning of the term "ligand" is inconsistent with the specification, particularly with respect to a complex comprising a heterodimer comprising a first and second polypeptide and a ligand, wherein no functionality is ascribed to the complex (e.g., it acts as a switch) or the ligand (e.g., it modulates binding of the first polypeptide to the second polypeptide).

The passage cited by Appellant states, "As applied to a protein switch, a ligand is any molecule capable of binding to the polypeptide biding molecule..." (Quoted in the first full paragraph on page 5 of the brief; emphasis added.)[4] Although the passage goes on to discuss examples of ligands that are known in the art, the passage in no way limits the ligand of the claim to the ligands discussed or presented in the cited art[5] and, in view of the unequivocal statement that "any molecule capable of binding the polypeptide binding molecule" is viewed as within the scope of a ligand, there is no reason to conclude that the plain meaning of the term

[4] The *prima facie rejection* cites the definition presented at p. 49, ll. 1-2 of the specification, "A ligand according to the invention is typically any molecule capable of binding to any of the other components of a switching system."
[5] It is noted that the art cited in the passage quoted by Appellant has not been made of record in the instant application and is not cited in the evidence appendix. Therefore, the art has not been considered beyond the characterization thereof in the specification.

ligand would be inconsistent with the meaning of ligand as used in the instant claim. Clearly any molecule that binds to the polypeptide binding component of the complex, including a zinc ion or even the DNA molecule to which the heterodimer binds, is reasonably within the scope of the ligand of the claim.

It is further noted: the passage at page 49, lines 16-28 of the specification cited by Appellant clearly refers to the use of the term ligand "[a]s applied to a protein switch..."; the passage at page 10, lines 16-19 of the specification[6], which defines the term "complex", does not require that a complex function as a switch; and the passage at page 10, lines 30-33 of the specification[7] defines a "protein switch" not a "complex" as recited in the instant claim. As noted in the *prima facie* rejection, the instant claim 34 has been expressly amended to remove all reference to protein switch function and ligand function. Therefore, teachings directed specifically to the properties of a protein switch do not limit the complex that is presently claimed, which is not required to function as a switch.

Likewise, with regard to Appellant's contention that that the ligand of the claim must mediate the binding of the two polypeptide molecules to each other, the disclosure does not contain any statement that the ligand comprised by a "complex" must mediate binding of the polypeptides of the complex and the claim has been amended to remove the function that was previously recited. In view of this and the fact that the complex as a whole need not exhibit any "switch" function, one of skill in the art would not conclude that the ligand of the claim must

[6] Quoted at page 5 of the Brief.
[7] Quoted at page 5 of the Brief.

mediate the binding of the two polypeptide molecules to each other as Appellant asserts.

"2. Barbas fails to describe or suggest a complex within the scope of claim 34."

Appellant contends that in rejecting claim 34 over Barbas, the Examiner has failed to take into account the enlightenment provided by the specification in regard to determining the correct meaning of the claim term "ligand." The broadest reasonable interpretation of this term, in the context of the complex of claim 34, is not a zinc ion coordinated by one of the two the DNA-binding polypeptides, but, rather a separate, molecular component that mediates interaction of the two DNA-binding polypeptides. Accordingly, Appellant concludes, the Zif(C7)6-Jun/Zif-268-Fos heterodimers disclosed by Barbas are not complexes as claimed because they lack a ligand component ligand component that mediates the binding of the two polypeptides in these complexes.

This argument has been fully considered but is not deemed persuasive. As discussed above, the zinc ion comprised Zif(C7)6-Jun/Zif- 268-Fos heterodimers disclosed by Barbas et al. is clearly within the scope of a "ligand" according to the plain meaning of the term, as would be the DNA molecule to which the polypeptides bind. Furthermore, as described herein above, nothing in the specification would lead one to conclude that the ligand of claim 34 must be construed contrary to its plain meaning. Appellant appears to believe that the requirement that the complex operate as a "switch" and that the ligand modulate the binding of the first and second polypeptide should be read into the claim even though these limitations were removed

from the claim in the Paper filed 14 August 2006. This would be wholly improper[8] given the plain meaning of ligand as the term would be understood in the art, given broad definition of a ligand provided in the specification even in the context of a "protein switch", and given the absence of any requirement that the claimed complex operate as a switch.

Appellant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claim is properly rejected under 35 USC § 102(b) as anticipated by Barbas et al.

"B. Claim 48 would not have been obvious over the cited references."

"1. Claim Construction: 'first' and 'second' polypeptides"

While acknowledging that the combination of Liu et al. and Vegeto et al. as indicated in the *prima facie* rejection would result in a combination that might have the capacity to form a homodimer containing two identical copies of a modified steroid receptor/zinc finger fusion protein, Appellant contends that the art does not read on the claimed invention because claim 48

[8] "Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment." *Superguide Corp. v. DirecTV Enterprises, Inc.*, 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004). See also *Liebel-Flarsheim Co. v. Medrad Inc.*, 358 F.3d 898, 906, 69 USPQ2d 1801, 1807 (Fed. Cir. 2004)(discussing recent cases wherein the court expressly rejected the contention that if a patent describes only a single embodiment, the claims of the patent must be construed as being limited to that embodiment); *E-Pass Techs., Inc. v. 3Com Corp.*, 343 F.3d 1364, 1369, 67 USPQ2d 1947, 1950 (Fed. Cir. 2003) ("Interpretation of descriptive statements in a patent's written description is a difficult task, as an inherent tension exists as to whether a statement is a clear lexicographic definition or a description of a preferred embodiment. The problem is to interpret claims in view of the specification' without unnecessarily importing limitations from the specification into the claims.") See MPEP 2111.01 II.

recites a system comprising a first polypeptide and a second polypeptide. Appellant contends that the terms must be construed to recite two different polypeptides in view of the Board Decision in Appeal No. 2006-1270 at pp.7-8. Appellant concludes, in view of this decision, even if the disclosures of Vegeto and Liu were combined, they would neither disclose nor suggest the heterodimer of claim 48.

This argument has been fully considered but is not deemed persuasive. As discussed above, during examination, the claims must be interpreted as broadly as their terms reasonably allow and it is improper to read limitations from the specification into the claims. The instant claim does not require that the switching system be a heterodimer even though the specification would support the limitation[9]. Although the Board decision in Appeal No. 2006-1270 construed first and second zinc finger protein as "two distinct and different zinc finger proteins" there is nothing in the decision to indicate the minimum "distinction and difference" required to distinguish two polypeptides as a "first polypeptide" and a "second polypeptide". In the instant case, there can be no question that a homodimer comprises two distinct polypeptides (i.e., they are comprised of different atoms and occupy different space at any given time). The instant claim does not specify that the first and second polypeptide exhibit any structurally or functionally unique property relative to the other polypeptide and there is no teaching in the specification to indicate that the first and second polypeptide cannot comprise the same amino acid sequence. Appellant's argument is based on an arbitrary determination that the minimum distinction and difference required in order to consider two polypeptides as "first" and "second" is that the

[9] Although Appellant offers to amend the claim to recite heterodimer, it is believed that the amendment would substantially change the scope of the claims such that a new finding of fact with respect to patentability of the claimed invention would be necessary. Therefore, the Examiner is not prepared to comment on the hypothetical claim.

polypeptides do not share the same amino acid sequence. However, Appellant's claim construction requires that one read into the claim limitations a limitation that is simply not stated anywhere in the disclosure. Furthermore, one of skill in the art would not have viewed the plain meaning of "first" and "second" as requiring that the first and second components do not share a common structure. For example, a similar interpretation of "a number set comprising a first number and a second number" would exclude the set "1, 1" because, although the set contains two numbers which occupy distinct and different positions in the set, the numbers are both "1". Clearly an interpretation of "a number set comprising a first number and a second number" which excludes all sets comprised of two of the same number is not the broadest reasonable interpretation. Likewise, given that the neither the claim nor the supporting disclosure require that the first and second polypeptide of a switching system be structurally different, the broadest reasonable interpretation of the claim is that the switching system is comprised of two polypeptides, which can differ from each other in any way (e.g., the atoms that they are comprised of or the space that they occupy at any given point in time). Thus, Appellant's assertion that the claim cannot read on a switching system comprised of a homodimeric complex is not consistent with the broadest reasonable reading of the claim.

"2. The rejection is improperly based on hindsight reconstruction"

Appellant contends that the Examiner has improperly based the obviousness rejection on a finding of what would be obvious in light of Appellants' disclosure. This assertion is wholly based on a statement made in the Advisory Action mailed 14 February 2007 wherein the Examiner, in discussing the teachings of the prior art, stated that it "would be obvious to use the

polydactyl DNA biding domain taught by Liu et al. in the modified steroid receptor taught by Vegeto et al." (14 February Advisory Action, page 4, first full paragraph). Appellant concludes, based on this sentence, that the rejection is based on a hindsight reconstruction of the prior art.

This argument is not persuasive because the record clearly shows that the finding of obviousness is based on the teachings available to the skilled artisan at the time the invention was made. For example, the *prima facie* rejection clearly states, "It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the molecular switch of Vegeto et al. to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu et al." (18 April 2006 Office Action, paragraph bridging pages 13-14.) Thus, the rejection is not based on an improper hindsight reconstruction, but on an analysis of what would have been obvious at the time the invention was made.

Appellant further asserts that the "common knowledge" relied upon in making this assertion has not been set forth. Rather, the rejection is founded upon an assertion that the nature of the problem to be solved by Vegeto is to regulate expression of a nucleic acid sequence in mammals, combined with Liu's disclosure of proteins theoretically capable of recognizing a unique site in a human genome.

This argument is not deemed persuasive. The motivation to combine the teachings of the prior art is stated in the 18 April 2006 Office Action as follows:

> It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the molecular switch of Vegeto *et al.* to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu *et al.* Motivation to combine these teachings comes from the nature of the problem to be solved by the molecular switch of Vegeto *et al.*, which is to regulate expression of a nucleic acid in mammals (*Id.*) and from the teachings of Liu *et al.* that: a) specific delivery of a DNA-binding protein to a single site within a genome as complex as that found

> in humans, 3.5 billion bp, requires an address of at least 16 bp (p. 5525, bridging col. 1-2); b) although natural proteins containing long polydactyl arrays of zinc-finger domains have been inferred from sequence, no zinc-finger proteins have been demonstrated to bind such a long contiguous DNA sequence (p. 5525, bridging col. 1-2); and c) the polydactyl proteins described therein can bind to a contiguous 18-bp DNA sequence with high affinity and specificity and function in human cells to activate or repress transcription.

The passage then goes on to explain why one of skill in the art would recognize an expected benefit of combining the elements disclosed in the teachings of the prior art in view of the teachings found therein:

> Viewed as a whole, the skilled artisan would clearly be motivated to substitute the polydactyl DNA binding domain of Liu *et al.* for the DNA binding domains contemplated by Vegeto *et al.* for construction of a molecular switch operative in mammalian cells to obtain the expected benefit of highly specific delivery of the switch in the complex mammalian genome.

In responding to Appellant's assertion in the Paper filed 1 February 2007 that the Office has not pointed to anything in either reference or the art as a whole that would motivate the skilled artisan to modify Vegeto's steroid receptor-containing to arrive at the subject matter of claim 48, the Examiner cites passages from MPEP 2143.01 and *Dystar* explaining that motivation can be implicit[10] in the teachings of the prior art. (14 February 2007 Advisory Action, pages 2-3.) The passage from the *prima facie* rejection quoted above explains why one of skill in the art would recognize an advantage in modifying the molecular switch of Vegeto *et al.* to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu *et al.* even

[10] Note that the Examiner has emphasized the word "implicitly" in quoting the passage from MPEP 2143.01. (14 February 2007 Advisory Action, page 2, paragraph 3.)

though the references do not explicitly state that the molecular switch of Vegeto et al. should comprise an engineered polydactyl Cys2-His2 zinc finger DNA binding domain. The Examiner's point is simply that motivation under 35 USC § 103 does not require that the art explicitly state that the teachings found therein should be combined.

"3. The record fails to show that dimerization of Vegeto's mutant glucocorticoid receptors is mediated by a ligand."

Appellant contends that the teachings of McEwan and Bledsoe do not evidence that dimerization of the modified steroid receptor of Vegeto is mediated by a ligand because McEwan, Bledsoe and the art as a whole actually teach is that the ligand mediates the dissociation of the receptor from a chaperone protein such as hsp90.

Appellant cites a passage from Bledsoe et al. that accurately describes the process of glucocorticoid (and other steroid hormone receptor) activation emphasizing the statement "the GR [glucocorticoid receptor] LBD [ligand binding domain] alone has been shown to be capable of forming a homodimer".[11] Appellant further cites Figure 2A of Bledsoe, which shows the structure of a GR dimer, with the dimerization interface at the center of the Figure and the ligand molecules (dexamethasone) well removed from the interface and thus not mediating dimerization. Appellant concludes that both McEwan and Bledsoe fail to teach that dimerization of steroid receptors is mediated by their ligand and consequently do not support the rejection.

This argument has been fully considered but is not deemed persuasive. Appellant's position appears to be based on a belief that the claim requires that the ligand participate directly

[11] Bridging pages 9-10 of the brief.

in the binding of the first polypeptide to the second polypeptide in the switching system (i.e., the ligand is a physical component of the binding interface). In contrast, the claim actually states, "the first polypeptide binds to the second polypeptide in a manner modulatable by a ligand". The claim does not in any way limit the manner by which binding of the first polypeptide to the second polypeptide is modulated. As described in the passages cited by Appellant, in the absence of ligand, steroid hormone receptors are sequestered by chaperone proteins such that they are unable to bind with one another. Upon ligand binding, the steroid hormone receptors are released from the chaperone proteins and bind to form dimers. Clearly, steroid hormones bind to one another in a manner modulatable by a ligand according to the proper interpretation of the claim limitations.

"4. There is no motivation to combine the references."

Appellant contends that the cited art fails to teach or suggest the protein switch of claim 48 because, "First and foremost, Vegeto does not teach a protein switch as claimed that comprises two different DNA binding domains whose interaction is mediated by a ligand. Rather, Vegeto teaches a molecular switch comprising a natural or modified steroid receptor DNA binding domain linked to a modified steroid receptor ligand binding domain (see, e.g., claims 32 and 33 of Vegeto)." (Brief, paragraph bridging pages 10-11.) Appellant concludes, Vegeto does not in any way teach or suggest that a ligand mediates interaction of two DNA binding domains, as required by claim 48.

Again, Appellant's argument is based on a reading of the claim that is not consistent with the actual wording of the claim. Appellant appears to be construing the claim as requiring that

the polypeptides of the switching system must comprise DNA binding domains that interact directly with each other. Furthermore, Appellant appears to view the claim as requiring that the ligand participate directly in the binding of the DNA binding domain of the first polypeptide with the DNA binding domain of the second polypeptide (i.e., the DNA binding domains interact directly and the ligand is a physical component of the binding interface). However, the claim does not recite that the switching system comprises "two different DNA binding domains whose interaction is mediated by a ligand." (Brief, paragraph bridging pages 10-11; emphasis added.) The claim recites that the system comprises a first polypeptide and a second polypeptide, wherein the first polypeptide binds to the second polypeptide in a manner modulatable by a ligand, and the first and second polypeptides bind to DNA. There is no limitation in the claim that the DNA binding domains comprised by the first and second polypeptides must interact directly with each other. Furthermore, as discussed above, the claim requires only that the polypeptides of the switching system bind to each other in a manner modulatable by a ligand and there is no limitation on the manner by which modulation is achieved. As described in the *prima facie* rejection, the prior art teaches every limitation required by the claim. The elements which Appellant contends distinguish the claimed invention from the prior art are simply not required by the claim as written.

Appellant further speculates that, because the ligand binding domain of steroid receptors contains sequences responsible for receptor dimerization (see, page 2, lines 25-27 of Vegeto) Vegeto's modification of this domain may destroy dimerization capability. Appellant notes that Vegeto is silent as to whether their mutant steroid receptors form homodimers, indicating instead that interaction with the ligand sufficiently "activates" the modified receptor

This argument has been fully considered but is not deemed persuasive. As clearly indicated in the evidence references (see, e.g., the passages from McEwin et al. and Bledsoe et al. quoted in Appellant's Brief at pages 9-10) activation of steroid hormone receptors involves dimerization of the receptor polypeptides. Furthermore, as pointed out by Appellant, Figure 2A of Bledsoe et al. shows the structure of a GR dimer with the dimerization interface at the center of the Figure and the ligand molecules (dexamethasone) well removed from the interface. (Brief, page 10, first paragraph following the quotation; emphasis added.) Still further, modifications to the ligand binding domain explicitly contemplated by Vegeto et al. are short C-terminal truncations of the polypeptide (see especially the first full paragraph on page 11). As shown in Figure 2 of Bledsoe et al., the C-terminus of the glucocorticoid receptor is on the opposite side of the protein relative to the protein-protein interaction interface. There is no evidence of record that would lead one of ordinary skill in the art to conclude that modifying the ligand binding domain as contemplated by Vegeto et al. would destroy dimerization given that the protein binding interface is, as Appellant admits, well removed from the ligand binding site and the explicitly contemplated C-terminal truncations would modify the protein in a region that is on the opposite side of the protein relative to the protein-protein interaction interface. Furthermore, given that operability of a switch requires that the chimeric receptors remain activatable and activation of steroid hormone receptors such as those used in constructing the switch of Vegeto et al. involves dimerization, one would clearly be motivated to retain the capacity to dimerize when constructing a switching system according to the teachings of Vegeto et al.

Appellant next urges that Liu relates to engineered zinc finger proteins and contains no reference to ligand-mediated interaction of two such zinc finger proteins and contends that,

because Liu et al. does not teach ligand-mediated interaction there is no reason to combine Liu with Vegeto as set forth by the Examiner. Appellant acknowledges that Liu relates to polydactyl zinc finger proteins for "unique addressing within complex genomes" but urges that Vegeto does not teach or suggest the desirability of addressing a unique site and accordingly there would not have been a motivation for one of skill in the art to combine the disclosures of Vegeto and Liu.

This argument has been fully considered but is not deemed persuasive. As pointed out in the *prima facie* rejection reiterated herein above, Vegeto et al. is teaching using the molecular switches disclosed therein to regulate expression in mammals (i.e. in the context of a mammalian genome) and Liu et al. teaches that the engineered zinc finger domains disclosed therein advantageously provide highly specific delivery of a switch even in the complex context of a mammalian genome. The primary reference used in making the rejection (Vegeto et al. as evidenced by McEwen et al. and Bledsoe et al.) teaches ligand-mediated interaction of two zinc finger proteins. Liu et al. is relied upon only for the teaching of engineered Cys2-His2 zinc finger binding domain and the advantages of the polydactyl zinc finger DNA binding domain described therein. The skilled artisan would perceive the benefit to be obtained by using the polydactyl zinc finger domains described by Liu et al. because, as Appellant acknowledges, Liu et al. teaches that the polydactyl zinc finger domains described therein provide for unique addressing within complex genomes and, as pointed out in the Final Office Action mailed 30 October 2006 (page 5), "The skilled artisan would perceive the benefit of specificity (i.e., avoiding artifacts due to off target expression) even if the switch of Vegeto et al. does not strictly require the use of a polydactyl zinc finger for operability."

Appellant concludes that the rejection is based on the improper test of what would be obvious, not what would have been obvious; that the Office has not pointed to anything in the references or the common knowledge available at the time of filing that would motivate the skilled artisan to modify Vegeto's steroid receptor to arrive at the subject matter of claim 48; that, at the time of filing, it was far from "common knowledge" that engineered zinc finger proteins could be used in dimerizing protein switches as claimed; and that a *prima facie* case of obviousness has not been made out because the Examiner's contention that the skilled artisan would have somehow had the knowledge modify Vegeto to employ Liu's proteins is completely unsupported by any reasoning "based on established scientific principles" that some advantage would have resulted from the hypothetical modifications. Appellant contends that it is only with Appellant's disclosure in hand that a skilled artisan would combine Vegeto and Liu.

These arguments have been fully considered but are not deemed persuasive. First, it is again noted that the *prima facie* rejection clearly states, "It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the molecular switch of Vegeto et al. to include the engineered polydactyl Cys2-His2 zinc finger DNA binding domain of Liu et al." (*Id.*) Thus, the standard used in making the rejection is clearly what would have been obvious at the time the invention was made. Furthermore, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). The rejection of record is wholly

based on teachings found in the prior art and what those teachings would have meant to one of ordinary skill in the art at the time the invention was made.

Contrary to Appellant's assertion, it was known in the art that that engineered zinc finger proteins could be used in dimerizing protein switches because that is precisely what Vegeto et al. is teaching. The only element of the claimed invention that is not taught by Vegeto et al. is an engineered Cys2-His2 DNA binding domain. However, it would have been obvious to one of ordinary skill in the art to modify the switching system taught by Vegeto et al. by including the Cys2-His2 binding domain taught by Liu et al. because, as repeatedly pointed out, Vegeto et al. is teaching the use of the switching system described therein in complex genomes and Liu et al. teaches that the polydactyl zinc finger domains described therein provide for unique addressing within complex genomes. Therefore, the skilled artisan would have perceived the benefit of specificity (i.e., avoiding artifacts due to off target expression in complex genomes) to be obtained by including the polydactyl zinc finger binding domains of Liu et al. in the switching system of Vegeto et al. Therefore, the claimed invention as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made.

"5. Vegeto teaches away from its combination with Liu."

Finally, Appellant contends that careful review of Vegeto's specification reveals that the only substitute DNA-binding domains suggested by Vegeto are non-mammalian DNA-binding domains. (Citing Vegeto at page 7, lines 7-12 and page 16, lines 14-1 8.) Appellant urges that, while Vegeto teaches substitution of non-mammalian DNA-binding domains for the DNA-binding domain of her mutant receptors, Liu teaches design of proteins for use in mammalian

cells (i.e., proteins theoretically capable of binding a unique site in a human genome). Thus, the references themselves teach away from their combination with each other, and this deficiency cannot be remedied by postulating some potential advantage to be gained by combining the two references.

This argument has been fully considered but is not deemed persuasive. While it is true that the substitute DNA binding domains suggested by Vegeto et al. are non-mammalian and Liu et al. teaches design of proteins for use in mammalian cells these teachings do not amount to a teaching away from combining the references. In particular, the teaching of Vegeto et al. that substitute DNA binding domains comprised by the switching system might be non-mammalian is not the same as a teaching that the switching system should not be used in mammalian cells. In fact, Vegeto et al. explicitly contemplates using the switching system in humans. (See, e.g., page 7, lines 20-27.) Furthermore, the polydactyl zinc finger DNA binding domain described by Liu et al. is not a mammalian DNA binding domain insofar as they are not naturally found in mammals. In addition, the polydactyl zinc finger DNA binding domain are specifically designed target specific binding sites within the context of a complex mammalian genome, which is precisely the intended use for the switching system of Vegeto et al. Therefore, contrary to Appellant's assertion, one of skill in the art would not have viewed the teachings of the cited art as teaching away from their combination.

Appellant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole. Therefore, the claim is properly rejected under 35 USC § 103(a) as

being unpatentable over Vegeto et al. as evidenced by McEwan et al. and Bledsoe et al. in view of Liu et al.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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